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How to Capture a Revolution

WHAT IS IT LIKE to try to capture the flavor and meaning of a revolution while you are in the middle of it? That is what Neil W. Toribara, MD, PhD, has tried to do in the medical staff conference, "Colorectal Cancer—A New Look at an Old Problem," elsewhere in this issue.[1] The understanding of colorectal carcinogenesis is rapidly being transformed by a multifaceted revolution in genetics and cellular biochemistry. The title of Toribara's review could just as easily have been "Colorectal Cancer—The New Look of an Old Problem" because this scientific revolution has converted the concept of colonic carcinogenesis from a relatively simple, multistep, histologic progression (the adenoma-carcinoma sequence) to a multidimensional process with histologic, biologic, genetic, and biochemical components.

The conceptual advances in the genetics and cellular biochemistry of colonic carcinogenesis have important clinical meaning for the prevention, early detection, and treatment of human colorectal cancer. Revolutions pose new challenges for all involved, and this one is no exception. The challenge for basic science and clinical investigators is to define the clinically useful components of the genetic and biochemical understanding of colonic carcinogenesis. The challenge for clinicians is to incorporate the useful concepts into the care of patients with or at risk for colorectal cancer.

As reviewed (and referenced) by Toribara,[1] several specific acquired genetic events—activation of the K-*ras* oncogene, inactivation of the putative tumor suppressor genes, *APC* ("adenomatous polyposis coli"), *DCC* ("deleted in colorectal cancer"), *P53*, and *hMSH2*—have become accepted as relevant to the process of colonic carcinogenesis. Exciting as these genetic discoveries are, they are only the beginning of the story. The depth of understanding of the cellular and biochemical consequences of these genetic alterations and the speed at which this field is advancing may not be as widely recognized.

Activation of the K-*ras* oncogene is a good example of the first point (depth of understanding). The normal K-*ras* gene codes for a 21-kd guanosine triphosphate (GTP)-binding protein called p21 that is critically positioned on the inner surface of the plasma membrane to function in transducing signals from the cell surface to intracellular targets. This protein is anchored to the plasma membrane by a lipid (farnesyl) intermediate that is added after translation. The biochemical details of at least one K-*ras*-dependent pathway have been recently described.[2] A simplistic description of the pathway is that epidermal growth factor binding to the transmembrane epidermal growth factor receptor results in tyrosine autophosphorylation of the cytosolic tail of the receptor. This tyrosine phosphorylation results in an interaction between two cytosolic proteins, GRB2 and SOS. The complex facilitates the release of guanosine diphosphate (GDP) from p21 (the K-*ras* gene product) and allows GTP to bind to p21. This GTP binding activates P21, and the activation initiates an intracellular kinase cascade (raf1, methylamino-purine [MAP] kinase kinase, MAP kinase) that ultimately results in transcriptional regulation. The normal p21 also has a guanosine triphosphatase (GTPase) activity that hydrolyzes bound GTP to GDP and inactivates p21, thus turning off the signal transduction pathway. Thus, the normal p21 plays a central role as an on-off switch (activation by GTP, inactivation by GTP hydrolysis) in regulating signal transduction. Mutations in K-*ras* occur in about 50% of colonic adenomas and carcinomas. The mutations are almost always point mutations in codons 12, 13, or 61 of the gene. These mutations result in a loss of the GTPase activity of p21, thus preventing inactivation of the signal transduction pathway. Cells with mutated K-*ras* can be viewed as having a constitutively activated signal transduction system. It is easy to imagine how constitutive activation of some signal transduction systems (growth factor systems) could result in a clone of cells with a growth advantage.

The detailed understanding of the biochemical consequences of K-*ras* mutations provides the basis for interventions to block the abnormality. At least two inhibitors of the farnesyl transferase that is required to properly anchor p21 to the plasma membrane have been developed and are being tested as chemopreventive or treatment agents in cell culture and animal systems.[3]

Although not all of the oncogene and tumor suppressor gene products are as precisely characterized as p21, a great deal is known about many of them, and the field is moving rapidly. The known functions of the genes frequently mutated in colon cancer are listed in Table 1. The common pattern of progress in this field is that the finding of genetic abnormalities in colonic cancers and adenomas led to the identification of the specific gene(s) involved, which allowed the identification and characterization of the relevant gene product. In some cases the precise function(s) of the gene products has been determined. It seems

ABBREVIATIONS USED IN TEXT

FAP = familial adenomatous polyposis
GDP = guanosine diphosphate
GTP = guanosine triphosphate
GTPase = guanosine triphosphatase
HNPCC = hereditary nonpolyposis colorectal cancer
MAP = methylaminopurine

likely that those findings will lead to biochemical (peptides or nucleotides) approaches to block carcinogenesis before direct genetic interventions become feasible.

The dramatic increase in the speed of the genetic and biochemical understanding of colonic carcinogenesis can be illustrated by the two strong familial colon cancer syndromes: familial adenomatous polyposis (FAP) and the hereditary nonpolyposis colorectal cancer (HNPCC) syndromes. Familial adenomatous polyposis was originally described in 1970 as a syndrome characterized by the development of thousands of adenomas.[4] Genetic linkage studies initially identified the location of the gene on chromosome 5 in 1987.[1] The *APC* gene was identified in 1991, and the precise gene function is being actively investigated (see Table 1). This seemed like rapid progress as it developed, but the pace of the HNPCC story has been stunning.

The initial HNPCC family was described in 1895 and "revisited" in 1971.[5] The HNPCC syndromes are characterized by the autosomal dominant inheritance of a gene that produces cancers of the colon and, in some families, other sites (endometrial, ovarian, gastric, brain). The colon cancers in these families tend to occur earlier than typical colon cancer (mean age 42), are often multiple, and occur predominantly (75%) in the proximal colon. A genetic locus responsible for some HNPCC families was reported in May 1993, and the chromosome 2 gene responsible for HNPCC (*hMSH2*) was reported in December 1993 (see Toribara for references[1]). A second genetic locus on chromosome 3 was linked to some HNPCC families in November 1993,[6] and the identification of the relevant gene (*hMLH1*) was reported in March 1994.[7] Germ-line mutations in the *hMSH2* and *hMLH1* genes are thought to be responsible for at least 50% of HNPCC families.

How can two distinct genetic defects lead to the same clinical syndrome? The two genes code for proteins that together are critical to the maintenance of integrity of the genome. The *hMSH2* gene is thought to identify and bind to mismatched base pairs that occur during DNA replication. The *hMLH1* gene is thought to bind to *hMSH2* and to coordinate the action of the enzymes that repair the mismatched DNA. The loss of function of either of these two gene products could easily result in a failure of point mutation repair and a markedly increased rate of mutation (genomic instability). In less than a year, we have progressed from knowing almost nothing about the genetic loci responsible for HNPCC to knowing the genetic sites, the genes involved, and their function—a remarkable pace!

Revolutions lead to challenges for both the participants and the rest of society. There is, in my view, a critical challenge for clinical investigations to keep pace with the advances in the basic understanding of colonic carcinogenesis. Classic types of clinical investigations of colorectal cancer have made substantial recent advances (see Toribara for references[1]). Epidemiologic and clinical studies have shown that a positive family history is an important risk factor for colonic adenomas and carcinomas and that this is likely due to the inheritance of susceptibility genes. Controlled prospective and case-control studies have for the first time demonstrated the effectiveness of screening with fecal occult blood tests and sigmoidoscopy. Controlled trials of the effectiveness of polypectomy in preventing colon cancer death and chemoprevention trials have demonstrated a dramatic regression of adenomas in

TABLE 1.—*Genes Frequently Mutated in Colon Cancer*

Gene	*Function of Gene Product*
K-*ras*	GTP binding protein; regulates signal transduction from cell surface receptors to intracellular targets; mutations lead to a constitutive activation of signal
APC	Germ-line mutation in familial adenomatous polyposis and Gardner's syndrome; interacts with catenin; may modulate cell-cell interactions; mutations thought to lead to a loss of function
DCC	Cell-surface protein; found abundantly in goblet cells; some homology to cell adhesion molecules; may modulate cell-cell interactions; mutations thought to lead to a loss of function
P53	Nuclear phosphoprotein; transacting transcription factor; controls cell replication by regulating proteins (cyclin and cyclin-dependent kinases) that are required for progression through the cell cycle (from G1 to S phase), prevents replication of cells with damaged DNA; promotes apoptosis in some cells; mutations lead to a loss of fidelity of DNA replication (genomic instability)
hMSH2	Germ-line mutation in some families with hereditary nonpolyposis colorectal cancer (HNPCC); recognizes mismatched nucleotides in DNA and initiates their repair; mutations lead to a rapid accumulation of genetic errors (genomic instability)
hMLH1	Germ line mutation in some families with HNPCC; probably binds to *hMSH2* and mediates the repair of mismatched nucleotides; mutations lead to rapid accumulation of genetic errors (genomic instability)

patients with familial polyposis after treatment with the nonsteroidal anti-inflammatory drug sulindac, although the mechanism of the effect is not yet known. Treatment trials have shown a benefit (albeit modest) for adjuvant therapy with fluorouracil and levamisole hydrochloride in Dukes' stage C colon cancer and with the combination of radiation therapy and chemotherapy in Dukes' stage B2 and C rectal cancer.[8] Chemoprevention trials have recently been launched to test the effectiveness of interventions—low-fat, high fruit and vegetable diet; fiber supplementation; nonsteroidal anti-inflammatory drugs; calcium; antioxidants—in the prevention of sporadic adenoma recurrence.

These are important advances, and their importance should not be understated, but a great deal more needs to be done. We now have an opportunity and a need to translate the basic science revolution into clinical practice. The potential effect of the new genetic and biochemical understanding of colonic carcinogenesis is broad, ranging from risk stratification, screening, and early detection to chemoprevention and treatment. It is now possible in most FAP families to use a blood test[1] to determine if a person has inherited the mutant *APC* gene and will have the clinical syndrome. The medical and ethical consequences of genetic diagnosis need to be evaluated. Do preventive measures instituted early affect the natural history of FAP? What is the optimal screening protocol for known gene carriers? What are the psychosocial and medicolegal consequences of a genetic diagnosis of FAP? Are there other genetic influences that alter the phenotype? What is the cellular function(s) that is (are) lost by mutation of the *APC* gene, and can it be biochemically or genetically restored to the cell?

A blood test capable of detecting gene carriers in at least some HNPCC families is expected to be commercially available soon. This will generate a series of important research questions comparable to those listed for FAP. Are more subtle alterations in the *APC* or *hMSH2* or *hMLH1* genes (or other definable genes) responsible for the familial predisposition to "sporadic" colorectal cancer?

We need to know if detecting the acquired genetic alterations that occur during carcinogenesis in stool, colonic lavage fluid, or randomly obtained biopsies can identify high-risk groups. Can rational preventive or treatment strategies based on the genetic and biochemical knowledge of colonic carcinogenesis be developed and clinically tested?

The number of interesting questions raised by this ongoing revolution seems endless. Clinical investigators need to help identify the most important questions and collaborate with the basic scientists to answer them. Basic scientists need to help find ways to apply their basic tools and assays to large clinical populations, and institutions must recognize the obstacles to this type of translational research and support mechanisms to facilitate it. Practicing clinicians will need to be aware of and support ongoing clinical trials; we will all need to understand and promptly take advantage of the clinically useful results of such trials. Finally, there is a major educational challenge for all of us because of the rapid expansion of the knowledge base. THE WESTERN JOURNAL OF MEDICINE can play an important role for its readers in this area.

Victor Hugo wrote, "Would you realize what revolution is, call it progress; and would you realize what progress is, call it tomorrow." I can hardly wait until tomorrow.

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